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(71) Applicant *(for all designated States except US)*: PHARMACIA & UPJOHN COMPANY [US/US]; 301 Henrietta Street, Kalamazoo, MI 49001 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: GAMMILL, Ronald, B. [US/US]; 38 Village Drive, East Lyme, CT 06333 (US). VANDER VELDE, Susan [US/US]; 6125 Fairgrove, Kalamazoo, MI 49009 (US). NUGENT, Richard, Allen [US/US]; 11358 East HJ Avenue, Galesburg, MI 49053 (US).

(74) Agent: YANG, Lucy, X.; Pharmacia & Upjohn Company, Intellectual Property Legal Services, 301 Henrietta Street, Kalamazoo, MI 49001 (US).

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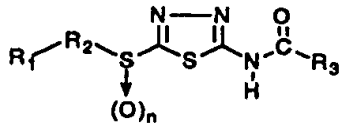

(I)

(57) Abstract

The present invention provides a compound of formula (I) wherein R_1, R_2 and R_3 are as defined herein. The compounds of the present invention are therapeutically useful in the treatment of a broad range of inflammatory disease such as, for example, hypersensitivity reactions, asthma, rheumatoid arthritis, bacterial meningitis, aspiration lung injury, inflammatory bowel disorder and related complications.

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THIADIAZOLES AMIDES USEFUL AS ANTIINFLAMMATORY AGENTS

FIELD OF THE INVENTION

This invention relates to novel thiadiazole amides, to pharmaceutical compositions containing them, and to methods of using them. The compounds of the invention are pharmaceutically active in the treatment of inflammatory diseases.

BACKGROUND OF THE INVENTION

Inflammation is an integral part of a wide array of human diseases, ranging from bacterial pneumonia, in which the response is life-saving, to adult respiratory distress syndrome, in which it is life-threatening. Inflammation may result in substantial tissue damage or initiate processes leading to excessive fibrous repair, and therefore, it is desirable to interrupt its progression. Today, many investigators are attempting to identify new therapeutic agents designed to directly block adhesive events involved in an array of disease processes.

LFA-1 and Mac-1, members of the β2 integrin family of adhesion molecules, are thought to play a critical role in several types of inflammatory disease processes by interacting with intercellular adhesion molecule (ICAM), which promotes the migration of the leukocyte rapidly into surrounding tissue. Support for the importance of β2 integrin in mediating inflammatory responses has been demonstrated by the evidence that transendothelial migration *in vitro* is markedly inhibited by monoclonal antibodies against β2 integrins or ICAM-1. C. W. Smith, *Can. J. Physiol. Pharmacol.*, Vol. 71, pp 76-87 (1993). Furthermore, blockade of the LFA-1 complex has been shown to inhibit neutrophil influx in almost every system, including skin, peritoneum, synovium, lung, kidney, and heart. As one of the primary ligands for the β2 integrins, it would also be expected that blockade of ICAM-1 would inhibit the inflammatory response. S. M. Albelda et al., *The FASEB J.*, Vol. 8, pp 504-512 (1994).

We now have discovered that certain novel thiadiazole amides are LFA-1 and Mac-1 inhibitors. Molecules that inhibit LFA-1 and Mac-1 binding with ICAM-1 down regulate inappropriate leukocyte wreaking havoc on healthy tissues seen in acute and chronic inflammatory diseases. As such, these compounds are therapeutically useful in the treatment of a broad range of inflammatory disease such as, for example, hypersensitivity reactions, asthma, rheumatoid arthritis, bacterial meningitis, aspiration lung injury, inflammatory bowel disorder and related complications.

INFORMATION DISCLOSURE

The following references disclose thiadiazole derivatives.

International Publication No. WO 96/30370 discloses thiazole and thiadiazole derivatives useful in the treatment of thrombocytopenia.

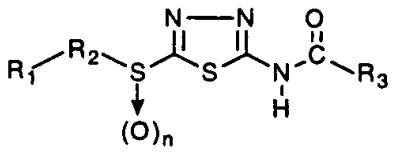
U. S. Patent 4,775,408 discloses pyridine substituted thiadiazole ureas which have herbicidal and plant growth regulatory properties.

U. S. Patent 4,576,629 discloses herbicidal thiadiazole ureas wherein the 5-position of the thiadiazole ring is hetero substituted and which exhibit enhanced selective herbicidal activity.

Abstract of Japanese Patent 1160-976-A discloses 1,3,4-thiadiazole derivatives useful as antiulcer agents.

SUMMARY OF THE INVENTION

The present invention presents novel compounds of formula I



I

or pharmaceutically acceptable salts thereof wherein:

R_1 is

a) -aryl,

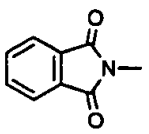
b) -aryl wherein aryl is substituted with one to three R_4,

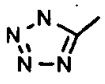
c) -Q,

d) -Q wherein Q is substituted with one to three R_4,

e) -Het,

f) -Het wherein Het is substituted with one to three R_4,

g)  ,

h)  , optionally substituted with C_{1-4} alkyl or C_{3-6} cycloalkyl,

i) C_{1-6} carboalkoxy,

j) $-C(=O)-CH_2CO_2(C_{1-4}$ alkyl), or

k) $-C(=O)NH(CH_2)_hR_5$,

l) C_{1-10} alkyl,

m) C_{1-10} alkyl substituted with one to three R_6,

n) C_{1-10} alkenyl, or

o) C_{1-10} alkenyl substituted with one to three R_6;

R_2 is

a) $-(C=O)_i(CH_2)_j(CR_7R_8)_k-$;

R_3 is

a) $-(CR_9R_{10})_l-(CH_2)_l$-aryl,

b) $-(CR_9R_{10})_l-(CH_2)_l$-aryl wherein aryl is substituted with one to three R_{11},

c) $-(CR_9R_{10})_l-(CH_2)_l$-Q,

d) $-(CR_9R_{10})_l-(CH_2)_l$-Q wherein Q is substituted with one to three R_{11},

e) $-(CR_9R_{10})_l-(CH_2)_l$-Het,

f) $-(CR_9R_{10})_l-(CH_2)_l$-Het wherein Het is substituted with one to three R_{11}, or

g) $-(CR_9R_{10})_l-(CH_2)_l$-pentafluorophenyl;

R_4 is

a) halo,

b) C_{1-4} alkyl,

c) C_{3-6} cycloalkyl,

d) C_{1-4} alkoxy,

e) aryl,

f) Q,

g) Het,

h) C_{1-4} carboalkoxy,

i) C_{1-4} monoalkylamino,

j) C_{1-4} dialkylamino,

k) amido,

l) C_{1-4} alkylthio,

m) trihalomethyl,

n) $-(CH_2)_l-O-(C_{1-4}$ alkyl),

o) nitro,

p) mercapto,

q) nitrine,

r) cyano,

s) hydroxy.

t) -NHC(=O)(C_{1-4} alkyl), or

u) -$NHSO_2$(C_{1-4} alkyl);

R_5 is

a) C_{1-8} alkyl,

b) aryl,

c) Q, or

d) Het;

R_6 is

a) halo,

b) hydroxy,

c) C_{1-4} alkoxy,

d) C_{1-4} carboalkoxy,

e) amido,

f) nitro,

g) trihalomethyl,

h) cyano,

i) mercapto,

j) C_{1-4} alkylthio, or

k) C_{1-8} alkyl;

R_7 and R_8 are the same and different and are

a) H,

b) C_{1-6} alkyl,

c) C_{3-6} cycloalkyl,

d) -$(CH_2)_l$-O-C_{1-4} alkyl,

e) -$(CH_2)_l$-Q, or

f) -$(CH_2)_l$-Het;

R_9 and R_{10} are the same and different and are

a) H,

b) C_{1-4} alkyl,

c) C_{1-4} alkoxy,

d) C_{3-6} cycloalkyl, or

e) C_{1-4} carboalkoxy;

R_{11} is

a) C_{1-4} alkyl,

b) C_{1-4} alkoxy,

c) trihalomethyl,

d) halo,

e) nitro,

f) cyano,

g) nitrine,

h) C_{1-4} acyl,

i) C_{1-4} carboalkoxy, or

j) carboxyl;

aryl is monocarbocyclic, or bicarbocyclic aromatic moiety;

Q is 5- to 10-membered saturated heterocyclic moiety having one to three atoms selected from the group consisting of oxygen, nitrogen, and sulfur;

Het is 5- to 10-membered unsaturated heterocyclic moiety having one to three atoms selected from the group consisting of oxygen, nitrogen, and sulfur;

h is 0, 1, 2 or 3;

i is 0 or 1;

j is 0, 1, 2, 3, 4 or 5;

k is 0, 1, 2 or 3;

l is 0, 1, 2, 3, 4 or 5;

n is 0, 1 or 2; and with the following provisos:

a) where both R_7 and R_8 are hydrogen, $j + k$ is other than 1;

b) where R_3 is phenyl substituted with fluoro, R_1 is other than unsubstituted phenyl.

These compounds are therapeutically useful in the treatment of a broad range of inflammatory disease such as, for example, hypersensitivity reactions, asthma, rheumatoid arthritis, bacterial meningitis, aspiration lung injury, inflammatory bowel disorder and related complications.

DETAILED DESCRIPTION OF THE INVENTION

For the purpose of the present invention, the carbon content of various hydrocarbon containing moieties is indicated by a prefix designating the minimum and maximum number of carbon atoms in the moiety, i.e., the prefix C_{i-j} defines the number of carbon atoms present from the integer "i" to the integer "j", inclusive. Thus, for example, C_{1-4} alkyl refers to alkyl of one to four carbon atoms, inclusive, or

methyl, ethyl, propyl, butyl and isomeric forms thereof.

The terms "C_{1-4} alkyl", "C_{1-6} alkyl", "C_{1-8} alkyl", and "C_{1-10} alkyl" refer to an alkyl group having one to four, one to six, one to eight, or one to ten carbon atoms respectively such as, for example, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl and their isomeric forms thereof.

The term "C_{2-10} alkenyl" refers to at least one double bond alkenyl group having two to ten carbon atoms respectively such as, for example, ethenyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, heptdienyl, octenyl, octadienyl, octatrienyl, nonenyl, undecenyl, dodecenyl, and their isomeric forms thereof.

The term "C_{3-6} cycloalkyl" refers to a cycloalkyl having three to six carbon atoms such as, for example, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl and their isomeric forms thereof.

The terms "C_{1-4} alkoxy" refers to an alkyl group having one to four carbon atoms attached to an oxygen atom of hydroxyl group such as, for example, methoxy, ethoxy, propyloxy, butyloxy and their isomeric forms thereof.

The term "C_{1-4} alkylthio" refers to an alkyl group having one to four carbon atoms attached to an thiohydroxy moiety, for example, methythio, ethylthio, propylthio, butylthio and isomeric forms thereof.

The terms "C_{1-4} acyl" and "C_{1-6} acyl" refer to a carbonyl group having an alkyl group of one to four or one to six carbon atoms respectively.

The terms "C_{1-4} carboalkoxy" and "C_{1-6} carboalkoxy" refer to an ester group having an alkyl group of one to four or one to six carbon atoms respectively.

The term "C_{1-4} monoalkylamino" refers to an alkyl group having one to four carbon atoms attached to an amino moiety, for example, methylamine, ethylamine, n-propylamine, n-butylamine, and isomeric forms thereof.

The term "C_{1-4} dialkylamino" refers to two alkyl groups having one to four carbon atoms attached to an amino moiety, for example, dimethylamine, methylethylamine, diethylamine, dipropylamine, methypropylamine, ethylpropylamine, dibutylamine, and isomeric forms thereof.

The term "halo" refers to fluoro, chloro, bromo, or iodo.

The term trihalomethyl refers to trifluoromethyl, trichloromethyl or tribromomethyl.

The term "aryl" refers to monocarbocyclic or bicarbocyclic aromatic moiety such as, for example phenyl, naphthyl or biphenyl. Each of these moieties may be substituted as appropriate. Aryl is preferably substituted and unsubstituted phenyl.

The term "Het" refers to a 5- to 10-membered unsaturated heterocyclic moiety

having one or more atoms selected from the group consisting of oxygen, nitrogen, and sulfur such as; for example, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 3-pyridazinyl, 4-pyridazinyl, 3-pyrazinyl, 2-quinolyl, 3-quinolyl, 1-isoquinolyl, 3-isoquinolyl, 4-isoquinolyl, 2-quinazolinyl, 4-quinazolinyl, 2-quinoxalinyl, 1-phthalazinyl, 2-imidazolyl, 4-imidazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 3-pyrazolyl, 4-pyrazolyl, 5-pyrazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 3-isothiazole, 4-isothiazole, 5-isothiazole, 2-indolyl, 3-indolyl, 3-indazolyl, 2-benzoxazolyl, 2-benzothiazolyl, 2-benzimidazolyl, 2-benzofuranyl, 3-benzofuranyl, benzoisothiazole, benzoisoxazole, 2-furanyl, 3-furanyl, 2-thienyl, 3-thienyl, 2-pyrrolyl, 3-pyrrolyl, 3-isopyrrolyl, 4-isopyrrolyl, 5-isopyrrolyl, 1-indolyl, 1-indazolyl, 2-isoindolyl, 1-purinyl, 3-isothiazolyl, 4-isothiazolyl and 5-isothiazolyl, preferably pyridyl, quionlinyl, pyrrolyl, thienyl, thiazolyl, or indolyl.

The term "Q" refers to a 5- to 10-membered saturated heterocyclic moiety having one to two atoms selected from the group consisting of oxygen, nitrogen, and sulfur such as, for example, piperidinyl, 2-, 3-, or 4-piperidinyl, [1,4]piperazinyl, morpholinyl, 2- or 3-morpholinyl, thiomorpholinyl, dioxolanyl, imidazolidinyl, [1,3]oxathiolanyl, [1,3]oxazolidinyl, pyrrolidinyl, butyrolactonyl, butyrolactamyl, succinimidyl, glutarimidyl, valerolactamyl, 2,5-dioxo-[1,4]-piperazinyl, pyrazolidinyl, 3-oxopyrazolidinyl, 2-oxo-imidazolidinyl, 2,4-dioxo-imidazolidinyl, 2-oxo-[1,3]-oxazolidinyl, 2,5-dioxo-[1,3]-oxazolidinyl, isoxazolidinyl, 3-oxo-isoxazolidinyl, [1,3]-thiazolidinyl, 2- or 4-oxo-[1,3]-thiazolidinyl, butyrolactamyl, succinimidyl, glutarimidyl, valerolactamyl, 2,5-dioxo-[1,4]-piperazinyl, 3-oxopyrazolidinyl, 2-oxo-imidazolidinyl, 2,4-dioxo-imidazolidinyl, 2-oxo-[1,3]-oxazolidinyl, 2,5-dioxo-[1,3]-oxazolidinyl, 3-oxo-isoxazolidinyl, 2- or 4-oxo-[1,3]-thiazolidinyl.

Within the definition of the terms "Het" and "Q", the nitrogen atom forming the hetero rings may have a protective group such as an acetyl or hydroxyacetyl group.

Certain reagents are abbreviated herein. THF refers to tetrahydrofuran, DMF refers to dimethyl formamide.

The compounds of the present invention can be converted to their salts, where appropriate, according to conventional methods.

The term "pharmaceutically acceptable salts" refers to addition salts useful for administering the compounds of this invention and include hydrochloride, hydrobromide, hydroiodide, sulfate, phosphate, acetate, propionate, lactate, mesylate, maleate, malate, succinate, tartrate, citric acid, 2-hydroxyethyl sulfonate, fumarate and the like. These salts may be in hydrated form. Some of the

compounds of this invention may form metal salts such as sodium, potassium, calcium and magnesium salts and these are embraced by the term "pharmaceutically acceptable salts."

Depending on substituents, the compounds of formula I of this invention may contain a chiral center and other isomeric forms and this invention embraces all possible stereoisomers and geometric forms.

Typical antiinflammatory thiadiazoles amides of this invention are

a. 3-Fluoro-N-[5-[(1-phenylpropyl)thio]-1,3,4-thiadiazol-2-yl]benzeneacetamide,

b. (E)-3-Nitro-N-[5-[(3,7-dimethyl-2,6-octadienyl)thio]-1,3,4-thiadiazol-2-yl]benzamide,

c. (E)-3-Trifluoromethyl-N-[5-[(3,7-dimethyl-2,6-octadienyl)thio]-1,3,4-thiadiazol-2-yl]benzamide,

d. N-[5-[[6-(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)hexyl]thio]- 1,3,4-thiadiazol-2-yl]-3-nitrobenzamide,

e. N-[5-[[6-(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)hexyl]thio]-1,3,4-thiadiazol-2-yl]-3-trifluoromethylbenzamide,

f. N-[5-[[6-(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)hexyl]thio]-1,3,4-thiadiazol-2-yl]-3-cyanobenzamide,

g. N-[5-[[6-(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)hexyl]thio]-1,3,4-thiadiazol-2-yl]-2,3,4,5,6-pentafluorobenzamide,

h. (E)-N-[5-[(3,7-Dimethyl-2,6-octadienyl)thio]-1,3,4-thiadiazol-2-yl]-2,3,4,5,6-pentafluorobenzamide,

i. (E)-N-[5-[(3,7-Dimethyl-2,6-octadienyl)thio]-1,3,4-thiadiazol-2-yl]-2,3,4,5,6-pentafluorobenzeneacetamide,

j. (E)-N-[5-[(3,7-Dimethyl-2,6-octadienyl)thio]-1,3,4-thiadiazol-2-yl]-2(3,4,5,6-pentafluorobenzene)propyl,

k. N-[5-[[2-Oxo-2-(4-pyridinyl)ethyl]thio]-1,3,4-thiadiazol-2-yl]-3-(trifluoromethyl)benzamide,

l. N-[5-[[2-Oxo-2-(3-pyridinyl)ethyl]thio]-1,3,4-thiadiazol-2-yl]-3-(trifluoromethyl)benzamide,

m. 3,4-Dichloro-N-[5-[[1-(3-pyridinyl)propyl]thio]-1,3,4-thiadiazol-2-yl]benzamide,

n. 3,5-Difluoro-N-[5-[[1-(3-pyridinyl)propyl]thio]-1,3,4-thiadiazol-2-yl]benzamide,

o. 3,5-Dimethoxy-N-[5-[[1-(3-pyridinyl)propyl]thio]-1,3,4-thiadiazol-2-yl]benzamide,

p. α -Methyl-N-[5-[[1-(3-pyridinyl)propyl]thio]-1,3,4-thiadiazol- 2-yl]benzeneacetamide,

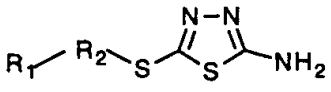
q. α-Cyclopropyl-N-[5-[(1-phenylpropyl)thio]-1,3,4-thiadiazol- 2-yl]benzeneacetamide, or

r. α-Methoxy-N-[5-[[1-(3-pyridinyl)propyl]thio]-1,3,4-thiadiazol-2-yl]benzeneacetamide.

The compounds of formula I are generally prepared by coupling an alkylating agent A

R' -halo (A)

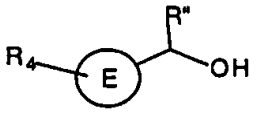
with commercially available 5-amino-1,2,5-thiadiazole-2-thiol in the presence of appropriate base such as, for example, triethylamine or sodium hydride. R' is R_1-R_2-radical as defined previously and halo is fluoro, chloro, bromo or iodo. The alkylating agents A are either commercially available or can be prepared from the corresponding alcohols with an activating agents such as methanesulfonyl chloride or thionyl chloride. The coupling results in the formation of the intermediate B



(B)

in the presence of an appropriate solvent such as, for example, THF, EtOAc, DMF, CH_3Cl or CH_3CN at room or slightly elevated temperature.

Particularly useful starting compounds in the preparation of compounds of formula I of the present invention is a compound of formula D



(D)

wherein R_4 is as defined previously, R" is R_7 or R_8 are as defined previously, the ring E is aryl, Q or Het as defined previously. All these starting compounds are either commercially available or can be easily prepared according to the methods well known in the art and are illustrated in examples as described hereinafter.

To provide compounds of formula I of the present invention, the intermediate B is converted to the corresponding thiadiazoles amides. Reaction of the intermediate B with acid chlorides, R_3COCl, in the presence of appropriate base such as triethylamine generates thiadiazole amides. The methods of these reactions are well known to those skilled in the art.

When desirable, the sulfur atom of the side chain can be oxidized by an appropriate oxidizer using the methods well known to those skilled in the art in an

early synthetic step or at the end of the synthetic sequence to the corresponding sulfones and sulfoxides, respectively.

The pharmaceutical compositions of this invention may be prepared by combining the compounds of formula I of this invention with a solid or liquid pharmaceutically acceptable carrier, and optionally, with pharmaceutically acceptable adjuvants and excipients employing standard and conventional techniques. Solid form compositions include powders, tablets, dispersible granules, capsules and suppositories. A solid carrier can be at least one substance which may also function as a diluent, flavoring agent, solubilizer, lubricant, suspending agent, binder, tablet disintegrating agent, and encapsulating agent. Inert solid carriers include magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, cellulosic materials, low melting wax, cocoa butter, and the like. Liquid form compositions include solutions, suspensions and emulsions. For example, there may be provided solutions of the compounds of this invention dissolved in water, water-propylene glycol, and water-polyethylene glycol systems, optionally containing conventional coloring agents, flavoring agents, stabilizers and thickening agents.

The pharmaceutical composition is provided by employing conventional techniques. Preferably the composition is in unit dosage form containing an effective amount of the active component, that is, the compounds of formula I according to this invention.

The quantity of active component, that is, the compounds of formula I according to this invention, in the pharmaceutical composition and unit dosage form thereof may be varied or adjusted widely depending upon the particular application method, the potency of the particular compound and the desired concentration. Generally, the quantity of the active component will range between 0.5% to 90% by weight of the composition.

In therapeutic use for treating inflammatory complications in humans and other animals that have been diagnosed with inflammatory disease, the compounds or pharmaceutical compositions thereof will be administered orally, parenterally, aerosol, and/or topically at a dosage to obtain and maintain a concentration, that is, an amount, or blood-level of active component in the animal undergoing treatment which will be antiflammatory effective. Generally, such antiinflammatory effective amount of dosage of the active component will be in the range of about 0.1 to about 200 mg/kg, more preferably about 3.0 to about 50 mg/kg of body weight/day. It is to be understood that the dosages may vary depending upon the requirements of the

patient, the severity of the inflammatory complication being treated, and the particular compounds being used. Also, it is to be understood that the initial dosage administered may be increased beyond the above upper level in order to rapidly achieve the desired blood-level or the initial dosage may be smaller than the optimum and the daily dosage may be progressively increased during the course of treatment depending on the particular situation. If desired, the daily dose may also be divided into multiple doses for administration, e.g., two to four times per day.

These compounds are useful for the treatment of inflammatory complications in humans and other warm blooded animals by either parenteral, oral, aerosol or topical administration. In general, the preferred form of administration is orally. Pharmaceutical compositions for parenteral administration will generally contain a pharmaceutically acceptable amount of the compounds according to formula I as a soluble salt (acid addition salt or base salt) dissolved in a pharmaceutically acceptable liquid carrier such as, for example, water-for-injection and a suitably buffered isotonic solution having a pH of about 3.5 - 6.0 Suitable buffering agents include, for example, trisodium orthophosphate, sodium bicarbonate, sodium citrate, N-methylglucamine, L(+)-lysine and L(+)-arginine, to name a few. The compounds according to formula I generally will be dissolved in the carrier in an amount sufficient to provide a pharmaceutically acceptable injectable concentration in the range of about 1 mg/ml to about 400 mg/ml. The resulting liquid pharmaceutical composition will be administered so as to obtain the above mentioned antiflammatory effective amount of dosage. The compounds of formula I according to this invention are advantageously administered orally in solid and liquid dosage forms.

The compounds of this invention are useful antiinflammatory agents, effective against a broad range of inflammatory disease states in which neutrophils wreak havoc on healthy tissues. Therefore, they are therapeutically useful in the treatment of chronic or acute inflammatory disease such as, for example, hypersensitivity reactions, asthma, rheumatoid arthritis, bacterial meningitis, aspiration lung injury, inflammatory bowel disorder and related complications. Humans or animals suffered with such complications are readily diagnosed by a physician or veterinarian of ordinary skill.

The compounds and their preparations of the present invention will be better understood in connection with the following examples, which are intended as an illustration of and not a limitation upon the scope of the invention.

I. Preparation of intermediate Compound B.

Method A:

5-Amino-1,3,4-thiadiazole-2-thiol (1 equiv.) is partially dissolved in CH_3CN. Triethylamine (2-3 equiv.) is added, followed by the alkyl chloride. The chloride is either commercially available, or generated from the alcohol with thionyl chloride (2 equiv.) in chloroform. The excess thionyl chloride is removed under reduced pressure, and the neat alkyl chloride was then added to the thiadiazole in CH_3CN. The reaction is stirred at 25-65°C overnight. The CH_3CN is removed *in vacuo*, and the residual oil is partitioned between $CHCl_3$ and H_2O. After the layers are separated, the aqueous phase is extracted with $CHCl_3$. The combined organics are washed with brine, dried over $MgSO_4$, and concentrated to crude material. Product is purified by either recrystallization or flash chromatography.

Method B:

The mesylate of the appropriate alcohol is prepared *in situ*. The alcohol (1 equiv.) is dissolved in THF, and triethylamine (2 equiv.) is added. The reaction is cooled to 0°C, and methanesulfonyl chloride (1.1 equiv.) is added. The reaction is allowed to warm to room temperature. After 1 hour, 5-amino-1,3,4-thiadiazole-2-thiol (1 equiv.) is added. The reaction is stirred overnight. The reaction is diluted with EtOAc and H_2O. After separation, the aqueous phase is extracted with EtOAc. The combined organics are washed with brine, dried over $MgSO_4$, and concentrated to crude material. The product is purified by flash chromatography or recrystallization.

Method C:

5-Amino-1,3,4-thiadiazole-2-thiol (1 equiv.) is dissolved in DMF and cooled to 0°C. Sodium hydride (1.1 equiv) is added, and the reaction is stirred at 0°C until all the solids are dissolved (1-2 hours). The alkyl chloride is generated from the alcohol (1 equivi) with thionyl chloride (2 equivi) in chloroform. The excess thionyl chloride is removed *in vacuo*. The alkyl chloride is added to the sodium anion of the thiadiazole. The reaction is allowed to warm to room temperature and stirred for 5-12 hours. The reaction is quenched and then diluted with H_2O. The aqueous solution is extracted with EtOAc, and the combined organics are washed with brine. After drying over $MgSO_4$, the solvent is removed *in vacuo* to yield crude material. The product is purified by flash chromatography or recrystallization.

Method D:

The appropriate alcohol (1 equiv.) and triethylamine (1.1 equiv.) is dissolved in THF and cooled to 0°C. Methanesulfonyl chloride (1.1 equiv.) is then added, and the reaction is stirred at room temperature for 1 hour. The reaction is diluted with

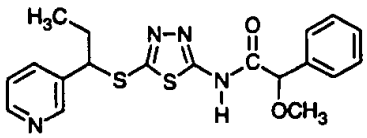
EtOAc and H_2O, and the layers are separated. The organic phase is washed with brine and dried over $MgSO_4$. The solvent is removed *in vacuo*, yielding pale yellow oil. The mesylate is added neat to the sodium anion of the thiadiazole. The thiadiazole is deprotonated by added sodium hydride (1.1 equiv.) to a 0°C solution of 5-amino-1,3,4-thiadiazole-2-thiol (1 equiv.) and dissolved in DMF. The reaction is allowed to warm to room temperature and stirred overnight. The reaction is quenched and diluted with H_2O. The aqueous phase is extracted with EtOAc, and the combined organics are washed with brine. After drying over $MgSO_4$, the solvent is removed *in vacuo* yielding crude material. The product is isolated by flash chromatography or recrystallization.

II. Preparation Thiadiazoles Amides.

Method E:

To a solution (or slurry) of alkylated thiadiazole (1 equiv.) in THF is added triethylamine or sodium hydride (2 equiv.). Next, acid chloride (1.1 equiv.) is added, and the reaction is stirred at room temperature for 5-12 hours. The reaction is diluted with CH_2Cl_2 and H_2O, and the layers are separated. The aqueous phase is extracted with CH_2Cl_2. The combined organics is washed with brine and dried over $MgSO_4$. Solvent is removed *in vacuo*, and the product is then purified by recrystallization or flash chromatography.

EXAMPLE 1 Preparation of α-Methoxy-N-[5-[[1-(3-pyridinyl)propyl]thio]-1,3,4-thiadiazol-2-yl]benzeneacetamide.



Step 1 Preparation of 5-[(1-pyridinylpropyl)thio]-1,3,4-thiadiazol-2-amine.

Following the general procedure outlined in Method B and making non-critical variations but starting with 1-phenylpropyl alcohol and 2-amino-5-mercapto-1,3,4-thiadiazole, the title compound is obtained as a solid. The crude product is purified by flash chromatography (5% CH_3OH/CH_2Cl_2). mp 113-114°C.

^1H NMR ($CDCl_3$) δ 0.94, 1.97-2.15, 4.40, 5.30, 7.25-7.31.

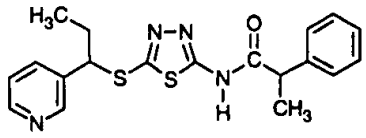
^{13}C NMR (DMSO) δ 11.8, 28.5, 54.9, 127.5, 127.7, 128.4, 140.5, 148.0, 170.4.

Following the general procedure outlined in Method E and making non-

critical variations but starting with the product of Step 1, Example 1 and α-methoxyphenyl acetyl chloride, the title compound is obtained as a solid.

^{1}H NMR (MEOH) 0.98, 1.98-2.19, 3.40, 4.63, 7.33-7.46, 7.84-7.88, 8.37, 8.44.

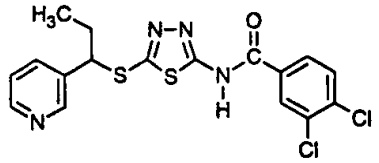
EXAMPLE 2 Preparation of α -Methyl-N-[5-[[1-(3-pyridinyl)propyl]thio]-1,3,4-thiadiazol- 2-yl]benzeneacetamide.



Following the general procedure outlined in Method E and making non-critical variations but starting with the product of Step 1, Example 1 and 2-phenyl proprionyl chloride, the title compound is obtained as a solid. mp 156-158°C.

^{1}H NMR (DMSO) 0.87, 1.40, 1.94-2.07, 3.98, 4.64, 7.23-7.36, 7.77-7.79, 8.42-8.44, 8.50.

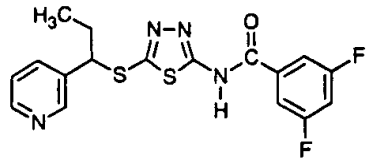
EXAMPLE 3 Preparation of 3,4-Dichloro-N-[5-[[1-(3-pyridinyl)propyl]thio]-1,3,4-thiadiazol-2-yl]benzamide.



Following the general procedure outlined in Method E and making non-critical variations but starting with the product of Step 1, Example 1 and 3,4-dichlorobenzoyl chloride, the title compound is obtained as a solid. mp 152-155°C.

^{1}H NMR (DMSO) 0.90, 1.97-2.12, 4.72, 7.34-7.38, 7.81-7.83, 7.98-8.02, 8.32, 8.44, 8.55.

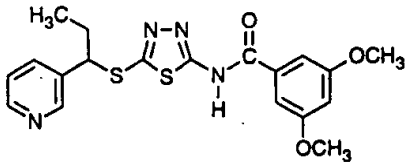
EXAMPLE 4 Preparation of 3,5-Difluoro-N-[5-[[1-(3-pyridinyl)propyl]thio]-1,3,4-thiadiazol-2-yl]benzamide.



Following the general procedure outlined in Method E and making non-critical variations but starting with the product of Step 1, Example 1 and 3,5-difluorobenzoyl chloride, the title compound is obtained as a solid. mp 174-177°C.

^{1}H NMR (DMSO) 0.90, 2.00-2.12, 4.73, 7.34-7.37, 7.57-7.63, 7.77-7.84, 8.44, 8.55.

EXAMPLE 5 Preparation of 3,5-Dimethoxy-N-[5-[[1-(3-pyridinyl)propyl]thio]-1,3,4-thiadiazol-2-yl]benzamide.



Following the general procedure outlined in Method E and making non-critical variations but starting with the product of Step 1, Example 1 and 3,5-dimethoxybenzoyl chloride, the title compound is obtained as a solid.
mp 169-171°C.

^{1}H NMR (DMSO) 0.90, 1.99-2.12, 3.79, 4.71, 6.74, 7.24-7.25, 7.34-7.28, 7.80-7.83, 8.44, 8.54.

INHIBITION OF β_2 INTEGRIN LIGAND BINDING ASSAYS

The compounds may be tested in one of several biological assays to determine the concentration of compound which is required to have a given pharmacological effect.

To identify inhibitors of β_2 integrin ligand binding function, two primary and two secondary assays are performed. The assays are established to identify compounds which inhibit the interaction of either LFA-1 or Mac-1 with immobilized ICAM-1. The interaction of the β_2 integrins with ICAM-1 plays as important role in a number of adhesive events during normal immune and inflammatory responses

including antigen presentation to T cells, T cell mediated cytotoxicity, and the firm attachment and extravasation of circulating leukocytes into the surrounding tissue. Both the primary LFA-1 and Mac-1 adhesion assays are performed using the well-known scintillation proximity assay (SPA) bead technology which is discussed in further in Cook, N.D. et. al. *Pharmaceutical Manufacturing International* (**1992**) pp. 49-53, "SPA: A revolutionary new technique for drug screening". Bosworth, N. and Towers, P. *Nature* (**1989**) 341:167-168, "Scintillation proximity assay". Undefriend, S., Gerber, L. and Nelson, N. *Analytical Biochemistry* (**1987**) 161: 494-500 "Scintillation Proximity Assay, a sensitive and continuous isotopic method for monitoring ligand-receptor and antigen-antibody interactions".

Briefly, the assay relies upon three major components: a radiolabeled CHO cell that has been transfected with the heterodimeric either LFA-1 or Mac-1 molecule and is functionally expressed on the cell surface; a secreted soluble form of intercellular ahesion molecule produced from a transfected CHO cell line and which has subsequently been biotinylated; and streptavidin SPA beads to monitor the interaction of these two components. The SPA technology is utilized because it obviates the need for a wash step(s), allowing low affinity interactions to remain undisturbed.

Stable CHO cells expressing either LFA-1 or Mac-1 were established. Cells were grown in modified Dulbecco's media and labeled overnight in a leucine deficient media in the presence of ^{3}H-leucine (10 mCi/10^{6} cells for LFA-1 and 50 mCi/10^{6} cells for Mac-1). After labeling, cells (1 x 10^{4} LFA-1 and 5 x 10^{4} for Mac-1) were activated with phorbol ester (100 nM for LFA-1 and 500 nM for Mac-1) and allowed to react with streptavidin SPA beads previously coated with biotinylated soluble ICAM-1 dispensed into 96 well plates. To inhibit adhesion to ICAM-1 coated SPA beads, 4X stock of compound, blocking antibodies or buffer control were added to the wells immediately prior to the addition of cells. Following incubation for 8 hours, adhesion was quantitated in the wells using a scintillation counter.

For further analysis of compounds that inhibit LFA-1 interactions, a secondary adhesion assay using JY and human soluble ICAM-1 was established. JY cells, a human lymphoblastoid cell line, constitutively expresses LFA-1. Microtiter wells were coated with soluble ICAM-1 diluted in 0.1 1M $NaCO_3$ buffer (pH 8.0) overnight at 4°C. The remaining binding sites on the plastic were blocked with phosphate buffered saline (PBS) containing 1 mM Ca^{2+}/Mg^{2+} and 1% human serum albumin (PBS/HSA) for 1 hour at 37°C. JY cells were harvested by centrifugation and fluorescently labeled with 2'7'-bis-(carboxyethyl)-5(6)-carboxy-fluorescien. JY

cells were then washed once in PBS/HSA, and stimulated with phorbol 12-myristate 13-acetate (PMA; 50 ng/ml) for 5 minutes. The microtiter plates was washed once with PBS containing 1 mM Ca^{2+}/Mg^{2+} and 0.5% Tween-20 and then immediately washed with PBS/HSA. A 80 mL aliquot of cells (1 x 10^5) was plated in triplicate on the microtiter wells. To inhibit adhesion to ICAM-1 coated wells, a 20 ml aliquot of 5X stock of compound, blocking antibodies or buffer control were added to the wells immediately prior to the addition of cells to the wells. Following incubation for 30 minutes at 37°C, the plates were washed with PBS/HSA. Fluorescence was quantitated in the wells using a Pandex fluorescence concentration analyzer.

For further analysis of compounds that inhibit Mac-1 interactions, a secondary adhesion assay using human neutrophils and human soluble ICAM-1 was established. Human neutrophils were used because of the limited availability of cultured cell lines expressing Mac-1. Mac-1 expressed on stimulated neutrophils play a major role in the adherence of neutrophils to endothelial cells and transendothelial migration via its interaction with ICAM-1. Microtiter wells were coated with soluble ICAM-1 diluted in 0.1 mM $NaCO_3$ buffer (pH 8.0) overnight at 4°C. The remaining binding sites on the plastic were blocked with PBS containing 1 mM Ca^{2+}/Mg^{2+} and 1% fetal calf serum (PBS/FCS) at room temperature for 30 minutes. Neutrophils were purified from the peripheral blood of healthy adult individuals by dextran sedimentation and centrifugation on a Ficoll-Hypaque solution. Neutrophils were then fluorescently labeled with 2'7'-bis-(carboxyethyl)-5(6)-carboxy-fluorescien. The cells were then washed in PBS/FCS and subjected to hypotonic lysis. To each well, 30 ml of PBS/FCS, 10 ml 10X stock of compound or blocking antibody, 10 ml f-Met-Leu-Phe (10^{-7}M), and 50 ml of cells (2 X 10^6 cells/ml) was plated in triplicate. Following incubation for 30 minutes at 37°C, the plates were washed with PBS. Fluorescence was quantitated in the wells using a Pandex fluorescence concentration analyzer.

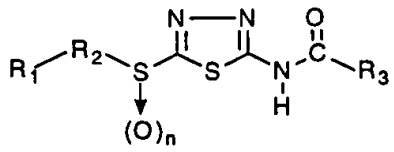
The inhibition results are given in Table 1. LFA/SPA and Mac-1/SPA refer to LFA-1 and Mac-1 adhesion assays are performed using the SPA technology; JY/ICAM refers to a secondary adhesion assay, inhibition of LFA-1 interactions, using JY and human soluble ICAM-1. PMN/ICAM refers to a secondary adhesion assay, inhibition of Mac-1 interactions, using human neutrophils and human soluble ICAM-1.

TABLE 1

Compound No.	LFA-1/SPA IC_{50} (μM)	Mac-1/SPA IC_{50} (μM)	PMN/ICAM IC_{50} (μM)	JY/ICAM IC_{50} (μM)
1	>20	>20	0.5	>20
2	10	8.9	10	>20
3	0.2	2.4	2.0	>20
4	2.3	16.9	2.0	>20
5	10	21.8	0.8	>20

We claim:

1. A compound of a formula I



I

or pharmaceutically acceptable salts thereof wherein:

R_1 is

a) -aryl,

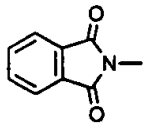
b) -aryl wherein aryl is substituted with one to three R_4,

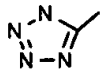
c) -Q,

d) -Q wherein Q is substituted with one to three R_4,

e) -Het, (172441 will be provisoed out)

f) -Het wherein Het is substituted with one to three R_4,

g)  ,

h)  , optionally substituted with C_{1-4} alkyl or C_{3-6} cycloalkyl,

i) C_{1-6} carboalkoxy,

j) $-C(=O)-CH_2CO_2(C_{1-4}$ alkyl)(172509),

k) $-C(=O)NH(CH_2)_hR_5$,

l) C_{1-10} alkyl,

m) C_{1-10} alkyl substituted with one to three R_6,

n) C_{1-10} alkenyl, or

o) C_{1-10} alkenyl substituted with one to three R_6;

R_2 is

a) $-(C=O)_i(CH_2)_j(CR_7R_8)_k-$;

R_3 is

a) $-(CR_9R_{10})_l-(CH_2)_l$-aryl,

b) $-(CR_9R_{10})_l-(CH_2)_l$-aryl wherein aryl is substituted with one to three R_{11},

c) $-(CR_9R_{10})_t-(CH_2)_t-Q$,

d) $-(CR_9R_{10})_t-(CH_2)_t-Q$ wherein Q is substituted with one to three R_{11},

e) $-(CR_9R_{10})_t-(CH_2)_t$-Het,

f) $-(CR_9R_{10})_t-(CH_2)_t$-Het wherein Het is substituted with one to three R_{11}, or

g) $-(CR_9R_{10})_t-(CH_2)_t$-pentafluorophenyl;

R_4 is

a) halo,

b) C_{1-4} alkyl,

c) C_{3-6} cycloalkyl,

d) C_{1-4} alkoxy,

e) aryl,

f) Q,

g) Het,

h) C_{1-4} carboalkoxy,

i) C_{1-4} monoalkylamino,

j) C_{1-4} dialkylamino,

k) amido,

l) C_{1-4} alkylthio,

m) trihalomethyl,

n) $-(CH_2)_t-O-(C_{1-4}$ alkyl),

o) nitro,

p) mercapto,

q) nitrine,

r) cyano,

s hydroxy.

t) $-NHC(=O)(C_{1-4}$ alkyl), or

u) $-NHSO_2(C_{1-4}$ alkyl);

R_5 is

a) C_{1-8} alkyl,

b) aryl,

c) Q, or

d) Het;

R_6 is

a) halo,

b) hydroxy,

c) C_{1-4} alkoxy,

d) C_{1-4} carboalkoxy,

e) amido,

f) nitro,

g) trihalomethyl,

h) cyano,

i) mercapto,

j) C_{1-4} alkylthio, or

k) C_{1-8} alkyl;

R_7 and R_8 are the same and different and are

a) H,

b) C_{1-6} alkyl,

c) C_{3-6} cycloalkyl,

d) $-(CH_2)_t-O-C_{1-4}$ alkyl,

e) $-(CH_2)_t-Q$, or

f) $-(CH_2)_t-Het$;

R_9 and R_{10} are the same and different and are

a) H,

b) C_{1-4} alkyl,

c) C_{1-4} alkoxy,

d) C_{3-6} cycloalkyl, or

e) C_{1-4} carboalkoxy;

R_{11} is

a) C_{1-4} alkyl,

b) C_{1-4} alkoxy,

c) trihalomethyl,

d) halo,

e) nitro,

f) cyano,

g) nitrine,

h) C_{1-4} acyl,

i) C_{1-4} carboalkoxy, or

j) carboxyl;

aryl is monocarbocyclic, or bicarbocyclic aromatic moiety;

Q is 5- to 10-membered saturated heterocyclic moiety having one to three atoms selected from the group consisting of oxygen, nitrogen, and sulfur;

Het is 5- to 10-membered unsaturated heterocyclic moiety having one to three atoms selected from the group consisting of oxygen, nitrogen, and sulfur;

h is 0, 1, 2, or 3;

i is 0 or 1;

j is 0, 1, 2, 3, 4 or 5;

k is 0, 1, 2 or 3;

l is 0, 1, 2, 3, 4 or 5;

n is 0, 1 or 2; and with the following provisos:

a) where both R_7 and R_8 are hydrogen, $j + k$ is other than 1;

b) where R_3 is phenyl substituted with F, R_1 is other than unsubstituted phenyl.

2. A compound of claim 1 which is

a. 3-Fluoro-N-[5-[(1-phenylpropyl)thio]-1,3,4-thiadiazol-2-yl]benzeneacetamide,

b. (E)-3-Nitro-N-[5-[(3,7-dimethyl-2,6-octadienyl)thio]-1,3,4-thiadiazol-2-yl]benzamide,

c. (E)-3-Trifluoromethyl-N-[5-[(3,7-dimethyl-2,6-octadienyl)thio]-1,3,4-thiadiazol-2-yl]benzamide,

d. N-[5-[[6-(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)hexyl]thio]- 1,3,4-thiadiazol-2-yl]-3-nitrobenzamide,

e. N-[5-[[6-(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)hexyl]thio]- 1,3,4-thiadiazol-2-yl]-3-trifluoromethylbenzamide,

f. N-[5-[[6-(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)hexyl]thio]- 1,3,4-thiadiazol-2-yl]-3-cyanobenzamide,

g. N-[5-[[6-(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)hexyl]thio]- 1,3,4-thiadiazol-2-yl]-2,3,4,5,6-pentafluorobenzamide,

h. (E)-N-[5-[(3,7-Dimethyl-2,6-octadienyl)thio]-1,3,4-thiadiazol-2-yl]-2,3,4,5,6-pentafluorophenylbenzamide,

i. (E)-N-[5-[(3,7-Dimethyl-2,6-octadienyl)thio]-1,3,4-thiadiazol-2-yl]- 2,3,4,5,6-pentafluorobenzeneacetamide,

j. (E)-N-[5-[(3,7-Dimethyl-2,6-octadienyl)thio]-1,3,4-thiadiazol-2-yl]- 2(3,4,5,6-pentafluorobenzene)propylamide,

k. N-[5-[[2-Oxo-2-(4-pyridinyl)ethyl]thio]-1,3,4-thiadiazol-2-yl]- 3-(trifluoromethyl)benzamide,

l. N-[5-[[2-Oxo-2-(3-pyridinyl)ethyl]thio]-1,3,4-thiadiazol-2-yl]- 3-(trifluoromethyl)benzamide,

m. 3,4-Dichloro-N-[5-[[1-(3-pyridinyl)propyl]thio]-1,3,4-thiadiazol-2-yl]benzamide,

n. 3,5-Difluoro-N-[5-[[1-(3-pyridinyl)propyl]thio]-1,3,4-thiadiazol-2-yl]benzamide,

o. 3,5-Dimethoxy-N-[5-[[1-(3-pyridinyl)propyl]thio]-1,3,4-thiadiazol-2-yl]benzamide,

p. α -Methyl-N-[5-[[1-(3-pyridinyl)propyl]thio]-1,3,4-thiadiazol- 2-yl]benzeneacetamide,

q. α-Cyclopropyl-N-[5-[(1-phenylpropyl)thio]-1,3,4-thiadiazol- 2-yl]benzeneacetamide, or

r. α-Methoxy-N-[5-[[1-(3-pyridinyl)propyl]thio]-1,3,4-thiadiazol-2-yl]benzeneacetamide.

3. A method of inhibiting LFA-1 and Mac-1 which comprises administering to a patient in need thereof an effective amount of a compound of claim 1.

4. A method of treating a patient suffering from inflammatory diseases which comprises administering to a patient in need thereof an effective amount of a compound of claim 1.

5. A method of claim 4 wherein the inflammatory diseases are hypersensitivity reactions, asthma, rheumatoid arthritis, bacterial meningitis, aspiration lung injury, inflammatory bowel disorder and related complications.

6. A pharmaceutical composition which comprises an effective amount of the compound of claim 1 and a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

Inter ›nal Application No
PCT/US 98/21629

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D285/135 C07D417/12 A61K31/41 A61K31/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 118, no. 5, 1 February 1993 Columbus, Ohio, US; abstract no. 34389d, CULLEN TG ET AL: "Nematicidal activity of 5-substituted-2-S-(3,4,4-trifluoro-3-butenyl)-1,3,4-thiadiazoles" page 229; XP002093613 see abstract -& DATABASE CHEMICAL ABSTRACTS ACS XP002093616 see RN 145070-02-6 & ACS SYMP. SER., vol. 504, 1992, pages 361-70, --- -/--	1

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 February 1999	02/03/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Allard, M

INTERNATIONAL SEARCH REPORT

Interr nal Application No
PCT/US 98/21629

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 83, no. 15, 13 October 1975 Columbus, Ohio, US; abstract no. 131514g, SHAMS-EL-DINE SA ET AL: "Chemical studies in the field of oral hypoglycemic agents. III" page 500; XP002093614 see abstract -& DATABASE CHEMICAL ABSTRACTS ACS XP002093617 see RN 56890-75-6, 56821-26-2, 56821-24-0, 56821-23-9 and 56821-22-8 & J. DRUG RES., vol. 6, no. 3, 1974, pages 203-7, ---	1,6
X	CHEMICAL ABSTRACTS, vol. 83, no. 25, 22 December 1975 Columbus, Ohio, US; abstract no. 206167g, SHAMS-EL-DINE SA ET AL: "Chemical studies in the field of oral hypoglycemic agents" page 385; XP002093615 see abstract & J. DRUG RES., vol. 6, no. 3, 1974, pages 103-8, ---	1,6
X	OKAWARA T ET AL: "A new route to 1,2,4-triazoles and 1,3,4-thiadiazoles from 1-acylbithiourea" JOURNAL OF HETEROCYCLIC CHEMISTRY, vol. 25, no. 4, July 1988, pages 1071-5, XP002093611 see the whole document, particularly page 1074, formulae 11a and 11b ---	1
X	KURZER F ET AL: "Heterocyclic compounds from urea derivatives. Part XXI. Adducts from thiocarbonohydrazides and aroyl isothiocyanates and their cyclisation" JOURNAL OF THE CHEMICAL SOCIETY, SECTION C,1971, pages 2932-8, XP002093612 see the whole document, particularly page 2938 ---	1
X	DATABASE CROSSFIRE Beilstein Institut für Literatur der organischen Chemie XP002093618 see BRN 562066 and 562078 & CROAT. CHEM. ACTA, vol. 33, 1961, page 121, 123 ---	1

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INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/US 98/21629

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CROSSFIRE Beistein Institut für Literatur der organischen Chemie XP002093619 see BRN 295534 & FARMACO ED. SCI., vol. 13, 1958, page 650, 659	1
A	US 5 668 159 A (JIN F ET AL) 16 September 1997 see the whole document	1-6

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 98/ 21629

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 3-5
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 3-5 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter. nal Application No
PCT/US 98/21629

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5668159 A	16-09-1997	NONE	